PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Commissioner
US Department of Commerce
United States Patent and Trademark
Office, PCT
2011 South Clark Place Room
CP2/5C24
Arlington, VA 22202
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 11 June 2001 (11.06.01)	
International application No. PCT/GB00/03575	**Applicant's or agent's file reference** N.79916A SMW
International filing date (day/month/year) 18 September 2000 (18.09.00)	**Priority date** (day/month/year) 17 September 1999 (17.09.99)
Applicant SHAW, David, Michael et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

12 April 2001 (12.04.01)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer Olivia TEFY
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	**FOR FURTHER ACTION**	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
N.79916A SMW		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/GB 00/03575	18/09/2000	17/09/1999
Applicant		
NEDERLANDSE ORGANISATIE VOOR TOEGEPAST ...		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 5 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

   a. With regard to the **language,** the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   [ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

   b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

   [ ] contained in the international application in written form.

   [ ] filed together with the international application in computer readable form.

   [ ] furnished subsequently to this Authority in written form.

   [ ] furnished subsequently to this Authority in computer readble form.

   [ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   [ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [ ] **Certain claims were found unsearchable** (See Box I).

3. [ ] **Unity of invention is lacking** (see Box II).

4. With regard to the **title,**

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract,**

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. _____

   [ ] as suggested by the applicant.

   [ ] because the applicant failed to suggest a figure.

   [ ] because this figure better characterizes the invention.

   [X] None of the figures.

INTERNATIONAL SEARCH REPORT

International Application No
P[illegible]B 00/03575

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K39/00 C12N15/74

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K C12N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
BIOSIS, CHEM ABS Data, MEDLINE, EPO-Internal, WPI Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	GRANGETTE, C. (1) ET AL: "Induction of mucosal and systemic immune responses after intranasal and intragastric immunization with recombinant Lactobacillus plantarum strains." IMMUNOLOGY LETTERS, (JUNE 15, 1999) VOL. 69, NO. 1, PP. 176. MEETING INFO.: 10TH INTERNATIONAL CONGRESS OF MUCOSAL IMUNOLOGY AMSTERDAM, NETHERLANDS JUNE 27-JULY 1, 1999, XP000914878 cited in the application the whole document --- -/--	1-4,7-9, 17,20, 21,24-30

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
23 January 2001	12/02/2001

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Charles, D

1

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	MAASSEN, CATHARINA B. M.: "A rapid and safe plasmid isolation method for efficient engineering of recombinant lactobacilli expressing immunogenic or tolerogenic epitopes for oral administration" J. IMMUNOL. METHODS (1999), 223(1), 131-136, XP002141071 page 131, column 1, paragraph 1 page 135, column 2, paragraph 2 page 133, column 2, paragraph 3 -page 135, column 1, paragraph 1 ---	1,12,16, 18-21, 23-29
X	MAASSEN, C. B. M. ET AL: "Instruments for oral disease-intervention strategies: Recombinant Lactobacillus casei expressing tetanus toxin fragment C for vaccination or myelin proteins for oral tolerance induction in multiple sclerosis." VACCINE, (APRIL 23, 1999) VOL. 17, NO. 17, PP. 2117-2128. , XP002158303	20,28,30
A	page 2118, column 2, paragraph 1 -page 2120, column 1, paragraph 2 page 2122, column 2, paragraph 2 page 2126, column 1, paragraph 1 - paragraph 2 page 2127, column 1, paragraph 2 - paragraph 3 ---	1,18,22
A	WELLS J M ET AL: "Lactic acid bacteria as vaccine delivery vehicles." ANTONIE VAN LEEUWENHOEK, (1996 OCT) 70 (2-4) 317-30. REF: 51, XP000914879 cited in the application	1,18
X	page 322, column 2, paragraph 1 page 323, column 1, paragraph 1 ---	20, 22-24, 28,29
A	POUWELS P H ET AL: "Lactic acid bacteria as antigen delivery vehicles for oral immunization purposes." INTERNATIONAL JOURNAL OF FOOD MICROBIOLOGY, (1998 MAY 26) 41 (2) 155-67. REF: 43, XP000921209 cited in the application	1,24
X	page 162, column 2, paragraph 1 -page 165, column 1, paragraph 1 --- -/--	18-22, 25,28-30

1

INTERNATIONAL SEARCH REPORT

International Application No
P[illegible]B 00/03575

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	WO 99 11284 A (TABAQCHALI SOAD ;WILKS MARK (GB); QUEEN MARY & WESTFIELD COLLEGE () 11 March 1999 (1999-03-11) cited in the application	1,18,24
X	page 2, line 12 -page 3, line 5; claims 1,10,11,20-23 page 8, line 16 - line 19 page 8, line 21 - line 25	20,21, 23,25-29
A	NL 8 700 890 A (TNO) 1 November 1988 (1988-11-01)	1,18,24
X	page 5, line 17 - line 27; claims 1,28-31 page 14, line 29 - line 34	20,25-29
A	HOLS P ET AL: "Efficient secretion of the model antigen M6-gp41E in Lactobacillus plantarum NCIMB 8826." MICROBIOLOGY, (1997 AUG) 143 (PT 8) 2733-41., XP000914880	1,6,24
X	page 2733, column 1, paragraph 2 -page 2734, column 1, paragraph 1 page 2739, column 1, paragraph 2	18,19
X	VAN DER ZEE, M. D. (1) ET AL: "Lactobacilli as live oral vaccine carriers against infection by rotavirus." IMMUNOLOGY LETTERS, (JUNE 15, 1999) VOL. 69, NO. 1, PP. 57. MEETING INFO.: 10TH INTERNATIONAL CONGRESS OF MUCOSAL IMUNOLOGY AMSTERDAM, NETHERLANDS JUNE 27-JULY 1, 1999 , XP000979035 the whole document	20,21, 25,28,29
X,P	SHAW, D. M. (1) ET AL: "Engineering the microflora to vaccinate the mucosa: Serum immunoglobulin G responses and activated draining cervical lymph nodes following mucosal application of tetanus toxin fragment C-expressing lactobacilli." IMMUNOLOGY, (AUGUST, 2000) VOL. 100, NO. 4, PP. 510-518. PRINT. , XP002158304 page 511, column 1, paragraph 1 page 511, column 2, paragraph 1 page 513, column 2, paragraph 1 -page 517, column 2, paragraph 2	1-10,12, 13,16-30

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1

INTERNATIONAL SEARCH REPORT

International Application No
P[redacted]B 00/03575

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	SLOS P ET AL: "Production of cholera toxin B subunit in Lactobacillus." FEMS MICROBIOLOGY LETTERS, (1998 DEC 1) 169 (1) 29-36., XP000914877 page 30, column 1, paragraph 1 - paragraph 2 page 35, column 2, paragraph 1 -----	1,5,18, 20,24,28

1

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
P[redacted]GB 00/03575

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9911284 A	11-03-1999	AU 8877998 A	22-03-1999
NL 8700890 A	01-11-1988	NONE	

PATENT COOPERATION TREATY

PCT

REC'D 15 JAN 2002
WIPO PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
N.79916A SMW		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/GB00/03575	18/09/2000	17/09/1999
International Patent Classification (IPC) or national classification and IPC A61K39/00		
Applicant NEDERLANDSE ORGANISATIE VOOR TOEGEPAST-... et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 11 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☒ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☒ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
12/04/2001	10.01.2002
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Leber, T Telephone No. +49 89 2399 7195

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/GB00/03575

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:
Description, pages:

1-41 as originally filed

Claims, No.:

1-30 as originally filed

Drawings, sheets:

1/2-2/2 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:

☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

II. Priority

1. ☐ This report has been established as if no priority had been claimed due to the failure to furnish within the prescribed time limit the requested:

☐ copy of the earlier application whose priority has been claimed.

☐ translation of the earlier application whose priority has been claimed.

2. ☐ This report has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid.

Thus for the purposes of this report, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:
see separate sheet

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-17,20,21,23-30
	No:	Claims	18,19,22
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-17,20,21,23-30
Industrial applicability (IA)	Yes:	Claims	1-24
	No:	Claims	

2. Citations and explanations
see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:
see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

Re Item II

Priority

1. Priority was checked and found valid for the relevant parts of the application which are covered by the intermediate document SHAW, D. M. (1) ET AL: 'Engineering the micro flora to vaccinate the mucosa: Serum immunoglobulin G responses and activated draining cervical lymph nodes following mucosal application of tetanus toxin fragment C-expressing lactobacilli.' IMMUNOLOGY, (AUGUST, 2000) VOL. 100, NO. 4, PP. 510-518. This P-document is therefore not relevant for the examination of the present application.

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive st p or industrial applicability; citations and explanations supporting such statem nt

1. Basis for the assessment of novelty, inventive step and industrial applicability

1.1 Reference is made to the following documents:

D1: MAASSEN, CATHARINA B. M.: 'A rapid and safe plasmid isolation method for efficient engineering of recombinant lactobacilli expressing immunogenic or tolerogenic epitopes for oral administration' J. IMMUNOL. METHODS (1999), 223(1), 131-136, XP002141071

D2: WO 99 11284 A (TABAQCHALI SOAD ;WILKS MARK (GB); QUEEN MARY & WESTFIELD COLLEGE () 11 March 1999 (1999-03-11) cited in the application

D3: POUWELS P H ET AL: 'Lactic acid bacteria as antigen delivery vehicles for oral immunization purposes.' INTERNATIONAL JOURNAL OF FOOD MICROBIOLOGY, (1998 MAY 26) 41 (2) 155-67. REF: 43, XP000921209 cited in the application

D4: HOLS P ET AL: 'Efficient secretion of the model antigen M6-gp41E in Lactobacillus plantarum NCIMB 8826.' MICROBIOLOGY, (1997 AUG) 143 (PT 8) 2733-41., XP000914880

D5: WELLS J M ET AL: 'Lactic acid bacteria as vaccine delivery vehicles.' ANTONIE VAN LEEUWENHOEK, (1996 OCT) 70 (2-4) 317-30. REF: 51, XP000914879 cited in the application

2. Novelty

2.1 Claim 1 of the present application appears to be novel (Art 33(2) PCT) as none of the documents cited in the ISR disclose a vaccine comprising L. plantarum expressing a heterologous antigen. The dependent claims 2-17 are thus also novel (Art 33(2) PCT).

2.2 Document D1 discloses the strain Lactobacillus plantarum 256 containing the plasmid pLP401-UreB or pLP401-TTFC, which encode for surface anchored UreB and tetanus toxin fragment C, respectively. None of these proteins are found in wild type L. plantarum 256 (D1, page 135, "3.4 Expression of heterologous..."; "3.5 Plasmid isolation from ..."). This strain was isolated from silage and is thus of "non-human" origin. Thus, claims 18 and 19 lack novelty (Art 33(2) PCT).

2.3 Document D2 discloses a vaccine comprising a Lactobacillus species such as L. plantarum NCIMB 8826 whereby the Lactobacillus is genetically modified to secrete the heterologous enzyme urease (D2, claims 1, 10; page 13, lines 6-27; page 11, line 14). The heterologous gene is encoded on a plasmid or may be inserted into the genome (D2, page 6, lines 25-26). The vaccine may be administered orally (D2, page 8, line 23) and upon administration to a mammalian species with said vaccine, an anti-urease immune response develops (D2, claims 1, 10).

The description of present application states that there is a "...lack of enablement of an oral vaccine using Lactobacillus as host...." in D2. However, D2 is not the only prior art document relating Lactobacilli with the concept of an oral vaccine. D3, for example, discloses lactic acid bacteria as antigen delivery vehicles for oral immunisation (D3, Title) and a vector for antigen presentation intracellularly, extracellularly and surface bound, which overcomes the problems of low expression observed with other vectors in, for example, L. plantarum (D3, page 162, "Genetic engineering of lactobacilli:..."; page 163 "7.1 Novel high efficiency Lactobacillus expression vectors"). Moreover, prior art document D4 discloses

that L. plantarum carrying the vector pNZα1 results in the release of the protein encoded on this plasmid. This suggests that release of the protein encoded on the related vector pNZα5 used in D2 is not as unlikely as described in the present application (page 4, line 26 - page 5, line 11). In conclusion, in spite of the lack of experimental data supporting the subject-matter disclosed in D2, it seems that, in view of the closely related prior art, the disclosure of D2 is sufficiently enabling for the skilled person (Art 5 PCT).

2.5 D2 does not explicity disclose the feature of L. plantarum NCIMB 8826 persisting in the gastro intestinal tract for more than 7 day. It appears, however, that this feature represents an intrinsic property of the said strain which is not altered by the heterologous gene expressed. Thus, in spite of the explicit disclosure, it appears that claim 22 lacks novelty (Art 33(3) PCT) over D2.

2.6 Claims 20, 21, 23-30 appear to be novel over the prior art cited in the ISR.

3. Inventive step

3.1 Claim 1 differs from the closest prior art document D2 (see 2.3 above) in that the heterologous antigen is either produced intracellularly or as cell surface protein. The technical problem is to provide an alternative presentation of the antigen. The solution referred to in claim 1, namely presentation of the antigen either intracellularly or as cell surface protein appears not to be inventive (Art 33(3) PCT) as it is common knowledge for the skilled person that an expressed protein may either be located intracellularly, at the cell surface or extracellularly. Moreover, these alternatives are also indicated in the prior art document D3 (D3, page 162, "Genetic engineering of lactobacilli:...").
Claims 2 and 24 lack an inventive step for the same reasons (Art 33(3) PCT).

3.2 Claim 20 refers to a non-human and/or non-human foodstuff derived Lactobacillus, which has been modified to express a heterologous antigen to enable it to elicit an immune response.
Claim 20 differs from the closest prior art document D2 in that the Lactobacillus is specified as being of non-human and/or non-human foodstuff origin. It appears that no technical effect is associated with this specification (page 9, line 28 - page

11, line 16). Thus, the technical problem is to provide an alternative Lactobacillus. It appears that the solution of a Lactobacillus being of non-human and/or non-human foodstuff origin referred to in claim 20 is a random selection lacking a technical contribution to the state of the art. Thus, an inventive step cannot be acknowledged (Art 33(3) PCT).
Claims 21, 26-28 lack an inventive step for the same reasons (Art 33(3) PCT).

3.3 Dependent claims 3-17, 23, 25, 29 and 30 appear not to contain features which in combination with the features of the claims to which they refer fulfil the requirements of Art 33(3) PCT for inventive step. The subject-matter of these claims appears to be disclosed in closely related prior art documents D1, D2, D5 or represents standard knowledge of the skilled person.

4. Industrial applicability

4.1 The subject-matter disclosed in the claims 1-24 of the present application appears to be industrially applicable (Art 33(4) PCT).

4.2 For the assessment of the present claims 25-30 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Re Item VI
Certain documents cited

1. The following document has an earlier priority and filing date than the present application but is not available in one of the official languages of the PCT. It appears however, that the subject matter the said document is relevant to the present application and it may therefore play a role in the examination of the present application in its regional or national phase.

a: NL-A-8 700 890 (TNO) 1 November 1988 (1988-11-01)

Re Item VII

Certain defects in the international application

1. The expression "herein incorporated by reference" or equivalents thereof (e.g. page 18, line 14) in the description of the present application should have been deleted (Guidelines, Section IV, II-4.17).

2. The description of the present application appears not to contain any explanation concerning the figures 1A-1D and the symbols used therein (Rule 5.1(a)(iv) PCT).

Re Item VIII

Certain observations on the international application

1. Claim 1 lacks clarity (Art 6 PCT) as the term "capable" appears to indicate that the bacterium used in the vaccine may or may not express the heterologous antigen. The description, however, appears to disclose that the heterologous protein is the antigen against which an immune response is to be established (page 1, lines 7-8). Similarly, the word "can" in the phrase "...and can elicit an immune response..." is unclear as this feature of inducing an immune response appears to be optional whereas the description appears to suggest that it is an essential part of the invention (page 1, lines 7-8). The same objection applies also to other claims, e.g. claims 2, 9 etc..

2. The oral vaccine referred to in claim 1 can "elicit [...] immunogenicity". It is unclear what is meant by this expression as the technical parameter of an antigen being immunogenic is an intrinsic feature of an antigen and commonly understood as the ability to induce an immune response. It is therefore unclear how immunogenicity can be elicited (Art 6 PCT). The same objection is raised against, for example, claim 4.

3. The Applicant is requested to delete terms such as "preferably" (e.g. claim 13),

"suitably" (e.g. claim 13), "such as" (e.g. claim 3) and "optionally" (e.g. claims 2, 3, 7 etc.) from the claims as the features following these expressions have no limiting effect on the subject-matter of the claim (Guidelines, Section IV, III-4.6).

4. Claim 4 of the present application refers to a pathogenic "microorganism". Claim 5 refers to claim 4 and provides a list of possible pathogens. Among these there are viruses, which are, by definition, no microorganism. Thus, claims 4 and 5 lack clarity (Art 6 PCT). The same objection applies also to claims 6, 7 etc. (Art 6 PCT).

5. The heterologous antigen in claim 4 is only defined by the result to be achieved, namely inducing immunogenicity against a pathogenic microorganism colonising the gastrointestinal tract. Criteria which permit to select such antigens are missing in claim 4. Thus, claim 4 lacks clarity (Art 6 PCT). The same objection applies to claim 9, which defines the vaccine by the feature that it "can induce protective immunogenicity" only (Art 6 PCT).

6. The abbreviations EHEC, ETEC, EIEC EPEC, EAggEC, DAEC in claim 5 lack clarity (Art 6 PCT). Moreover, several pathogenic microorganisms are defined by a certain behaviour ("...possess enteroinvasiveness...") or by their ability to cause a particular disease ("...causing malaria..."; "...causing toxoplasmosis...") only, resulting in a lack of clarity (Art 6 PCT).

7. Claim 11 defines the level of expression of the heterologous protein in comparison to the level of expression of β-galactosidase in L. plantarum 80. As the latter is unknown, claim 11 lacks clarity (Art 6 PCT).

8. The persistence of the recombinant L. plantarum appears to be an intrinsic feature of the strain due, for example, to its ability to adhere to the gastro intestinal epithelium (see, for example, D5, page 319, Table 1) and appears to be independent of the heterologous gene expressed. Thus, claim 13 lacks clarity (Art 6 PCT) as to which feature is added to the subject-matter. Moreover, it can be expected that the persistence is species dependent resulting in a lack of support by the description (Art 6 PCT). The same objection applies to claim 14.

9. The term "equivalent conditions" in claim 14 lacks clarity (Art 6 PCT). Moreover, claim 14 defines the persistence of a vaccine encompassing L. plantarum by its persistence being longer than that of L. plantarum 80 and L. plantarum NCIMB 8826. These features lack clarity (Art 6 PCT) as the persistence of the latter two strains is not disclosed in the present application. In addition, as it can be expected that the persistence is dependent on the species vaccinated, claim 14 appears to lack support by the description over its full scope (Art 6 PCT).

10. In claim 15 a word appears to be missing (Art 6 PCT).

11. The phrase "A bacterium...of non-human origin" in claim 18 lacks clarity (Art 6 PCT). What appears to be meant is that the bacterium was not isolated from a human. The same objection applies to claim 20 (Art 6 PCT).

12. Claim 20 appears to lack support by the description (Art 6 PCT) as the description seems to support only modification of lactobacillus by inserting a vector. An insertion of the heterologous gene into the genome appears not to be supported by the description (Art 6 PCT).

13. Claim 21 refers to a L. plantarum which is "foreign to that individual or is not present in the G.I. tract or mucosa of humans". It is unclear in what context the term "foreign" has to be seen (Art 6 PCT). Moreover, the abbreviation "G.I." lacks clarity and should be defined (Art 6 PCT). The latter objection is also raised against claim 27.

14. Claims 25 and 28 refer to a bacterium according to claims 19-24. Claim 24, however, refers to a plasmid, resulting in a lack of clarity (Art 6 PCT).

15. Claims 5, 7, 24, 27 etc. contain features written in brackets (e.g. "...(the strain is endogenous)...") resulting in a lack of clarity (Art 6 PCT) regarding whether or not these features are optional.